Claims 53-57 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 15, 28-30, and 32 of copending Application No. 08/643,732. Since this is a provisional rejection, applicants respectfully request that the rejection be held in abeyance.

Claims 48-93 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to the skilled artisan that applicants had possession of the claimed invention at the time the application was filed. The Examiner contends that the few disclosed embodiments are not representative of the products claimed. The Examiner disregards Dr. Choulika's Declaration as disclosing chimeric, but not necessarily transgenic, mice.

Applicants traverse the rejection. The mere presence of a Group I endonuclease recognition site is all that is required of applicants' transgenic mice comprising a Group I endonuclease recognition site. A Group I endonuclease recognition site is small and does not "express" anything itself. Endonucleases specific for Group I encoded endonuclease sites do not exist naturally in mice. Consequently, the mere presence of a Group I encoded endonuclease site should have no specific phenotypic consequence. The attached Second Declaration of Andre Choulika supports this conclusion. Accordingly, a mouse comprising a Group I endonuclease recognition site should have the same wild-type phenotype as a mouse containing an I-*Sce*I site.

Applicants described the insertion of a representative species of Group I endonuclease recognition site, I-*Sce*I, into mouse D3 cells for making transgenic mice. (Specification at 38.) As indicated in Dr. Choulika's Declaration dated October 8, 2001, applicants' D3 cells were able to generate transgenic mice.

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The Examiner alleges that Dr. Choulika's Declaration only indicates that the mice containing an I-*Sce*I site were chimeric with a phenotypic expression ranges of 50-80%, but not transgenic. Applicants disagree.

Applicants' chimeric mice are transgenic. Transgenic mice need to carry exogenous DNA to be transgenic, but that DNA need not be germ line transmissible. As objective evidence to support this conclusion, applicants have attached Exhibits 1-4, which provide definitions for transgenic animals. None of these definitions requires germ line transmission for an animal to be transgenic. Accordingly, the mice containing an I-*Sce*I site described in Dr. Choulika's Declaration were transgenic mice.

In addition, the Examiner has provided no reasons to doubt the ability to obtain transgenic mice with germ line transmission once chimeric mice with phenotypic expression ranges of 50-80% have been obtained. Prior to applicants' invention, mouse ES cells were routinely used to make transgenic mice, both chimeric mice and mice with germ line transmission. For example, Zijlstra et al., 1989 (Exhibit 5), used D3 ES cells to make transgenic mice. Zijlstra et al. were able to obtain germ-line transmission from most of the chimeric mice with 50-95% coat color chimerism. Zijlstra et al. at Table 2. Similarly, Gossler et al., 1986, (Exhibit 6), used D3 ES cells to make transgenic mice. Gossler et al. were able to obtain 50-75% germ-line transmission from the fertile chimeric male mice with 30-50% coat color chimerism. Gossler et al. at 9067, column 1, first paragraph. Robertson et al., 1986 (Exhibit 7) used XY stem cell line EK.CCE to make transgenic mice. Robertson et al. bred 16 phenotypically male chimeras and obtained germline transmission of the transgene from 6 of 13 fertile mice. Robertson et al. at 446, column 1, second paragraph. Joyner et al., 1991 (Exhibit 8), indicated that CCE and D3 cell lines contribute to the germ line **at high frequency**. Joyner et al. at

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650, column 2, first paragraph. Joyner et al. concluded that "germline transmission . . . seems likely as long as two or three targeted ES cell clones are available." Joyner et al. at 654, column 2, first paragraph. Thus, at the time the invention was made, the skilled artisan would have concluded that once a chimeric mouse containing a Group I encoded endonuclease site was generated, generation of an animal having germline transmission of the Group I encoded endonuclease site would require no more than routine screening. The attached Second Declaration of Andre Choulika further supports the conclusion that, once a chimeric mouse containing a Group I encoded endonuclease site is generated, generation of an animal having germline transmission of the Group I encoded endonuclease site would require no more than routine screening. Accordingly, the skilled artisan would have immediately recognized that applicants had possession of the claimed transgenic mice at the time the application was filed.

The Examiner has provided no reasons why the generation of a mouse comprising an I-*Sce*I site is not representative of the generation of mice with any Group I endonuclease recognition site. A mouse comprising an I-*Sce*I site would have the same wild-type phenotype as a mouse containing another Group I endonuclease recognition site. The attached Second Declaration of Andre Choulika attests to the lack of any specific negative effect of a Group I encoded endonuclease site on the phenotype of a transgenic mouse. The Declaration also attests to the predictability of generating mice comprising Group I endonuclease recognition sites. Therefore, applicants' working example is representative of the insertion of any and all Group I endonuclease recognition sites. Accordingly, there can be no doubt that applicants had possession of mice comprising any and all Group I endonuclease recognition sites.

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Furthermore, having read applicants' specification, the skilled artisan expects that the insertion of a Group I endonuclease recognition site in mice is a predictable event. The attached Second Declaration of Andre Choulika supports this conclusion.

Applicants' disclosed embodiments are representative of the claimed invention. Applicants' description of the claimed transgenic mice in the specification reasonably conveys to the skilled artisan that applicants had possession of the claimed mice at the time of filing. Accordingly, applicants' description is sufficient to fulfill 35 U.S.C. § 112, first paragraph, and applicants respectfully request withdrawal of the rejection.

Claims 48-93 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter that was not described in the specification in such a way as to enable the skilled artisan to make and/or use the invention. The Examiner contends that the phenotype of a transgenic animal is determined by a complex interaction of genetics and environment, and that it is difficult to predict the behavior of a transgene in any and all animals. The Examiner concedes that the skilled artisan would have been able to make the required genetic constructs encoding any and all Group I encoded endonuclease sites. However, the Examiner concludes that it would have required an excessive and undue amount of experimentation to generate transgenic mice encoding any and all Group-I intron encoded endonuclease sites without a predictable degree of success.

Applicants traverse the rejection. The Examiner's position is based on an alleged unpredictability of the **phenotype** of transgenic animals. The references cited by the Examiner are directed towards supporting the unpredictability of the **phenotype** of transgenic animals. However, these references are not relevant to applicants' claimed invention since the phenotype of applicants' claimed transgenic mice is predictable. That is, the skilled artisan expects applicants' claimed mice to have a wild-type phenotype.

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Therefore, the Examiner's position that applicants' claimed transgenic mice are not predictable is unsupported.

The attached Second Declaration of Andre Choulika indicates that the presence of a Group I encoded endonuclease site in a transgenic mouse should not have any specific negative effect on the phenotype of the transgenic mouse. The Declaration indicates that these transgenic mice should have a predictable phenotype: wild-type.

In order to make a rejection for lack of enablement under 35 U.S.C. § 112, first paragraph, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 1562, 27 U.S.P.Q.2d. 1510, 1513 (Fed. Cir. 1993). According to *In re Bowen*, 181 U.S.P.Q. 48, 51 (CCPA 1974), the minimal requirement is for the Examiner to give reasons for the uncertainty of the enablement. The Examiner has not met this burden since the Examiner has not provided any reasons relevant to applicants' claimed mice containing a Group I intron encoded endonuclease site.

In contrast to the Examiner's lack of a reasonable basis to question applicants' enablement, applicants have previously submitted objective evidence supporting the predictability of applicants' claimed invention. (*See, e.g.*, Applicants' January 27, 2000, Response to Paper No. 5.) Applicants provided a Declaration from Dr. Choulika attesting to the generation of mice following the teachings of the specification. Applicants further submit herewith Exhibits 5-8, which discuss the generation of transgenic mice from ES cells. These Exhibits attest to the predictability and routine nature of generating transgenic mice from ES cells at the time the application was filed.

The attached Second Declaration of Andre Choulika indicates that that the generation of transgenic mice having a Group I endonuclease recognition site is a

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predictable event. All of this evidence supports the predictability of generating transgenic mice containing a Group I intron encoded endonuclease site following applicants' teachings. Accordingly, applicants submit that the claimed invention is fully enabled and respectfully request withdrawal of the rejection.

Applicants respectfully submit that this application is in condition for allowance. In the event that the Examiner disagrees, he is invited to call the undersigned to discuss any outstanding issues remaining in this application in order to expedite prosecution.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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